REMARKS/ARGUMENTS

With this amendment, claims 1-19, 27-45, 53 and 54 are pending. Claims 20-26, 28-38, and 45-53 are cancelled. Claim 13 is withdrawn. For convenience, the Examiner's rejections are addressed in the order presented in an August 23, 2006, Office Action.

I. Status of the claims

Claims 1 and 27 are amended to recite 95% identity to full length SEQ ID NO:4. Support for these amendments is found throughout the specification, for example at page 7, line 29-page 8, line 14. Claims 1 and 27 are also amended to recite identifying a compound that inhibits angiogenesis in the preamble and in clause (ii). Support for this amendment is found throughout the specification, for example, at Figures 13, 15, and 17. Claim 27 is also amended to recite that down regulation of the angiogenesis polypeptide inhibits angiogenesis. Support for this amendment is found throughout the specification, for example, at page 9, lines 19-23; page 30, lines 9-10; page 31, lines 23-25; and page 48, line 20 through page 49, line 20. The specification also provides experimental evidence of down regulation of the Axl polypeptide that inhibits angiogenesis, *e.g.*, at Figures 12, 14, 15, and 17, which show that an Axl specific RNAi down regulates Axl expression resulting in inhibition of angiogenesis as measured by haptotaxis or tube formation assays. These amendments add no new matter.

Claims 10, 19, and 45 are amended to correct grammatical errors. Claim 53 is cancelled and claim 54 is amended to depend from claims 1 or 27. These amendments add no new matter.

II. Objections to the claims

Claims 19 and 45 are objected to for an alleged informality. In order to expedite prosecution, claims 19 and 45 are amended as directed by the Office Action. In view of this amendment, withdrawal of the claim objections is respectfully requested.

III. Rejections under 35 U.S.C. §112, second paragraph

Claims 1-12, 14-19, 27-37, 40-45, and 54 are rejected for alleged indefiniteness. Claim 10 is amended to correct a grammatical error. In order to expedite prosecution, independent claim 1 is amended to relate the process steps to the preamble by reciting the phrase "thereby identifying the compound that modulates angiogenesis" in the final clause. In order to expedite prosecution, independent claim 1 is amended to relate the process steps to the preamble by reciting the phrase "thereby identifying the compound that modulates tumorigenesis" in the final clause.

In view of these amendments, withdrawal of the rejections under 35 U.S.C. §112, second paragraph is respectfully requested.

IV. Rejections under 35 U.S.C. §112, first paragraph, enablement

The Office Action present five rejections for alleged lack of enablement. Each rejection is discussed below using the relevant paragraph heading from the Office Action.

A. Paragraph 8

Claims 1-12, 14-19, 53, and 54 are rejected for alleged lack of enablement. According to the Office Action, the claims are enabled for the use of an Axl polypeptide comprising SEQ ID NO:4, but are allegedly not enabled for use of Axl polypeptides that comprise amino acid sequences with 90 or 95% identity to SEQ ID NO:4. Although the unamended claims recite an Axl polypeptide that comprises SEQ ID NO:4 or a polypeptide with 90% or 95% identity to SEQ ID NO:4, the Office Action appears to assert that the claims read on any polypeptide that comprises 60% of a 25 amino acid sequence fragment of SEQ ID NO:4. See, *e.g.*, Office Action at page 6 and 7. In discussion of the Axl protein, the Office Action also alleges that little is known about that protein. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

Factors such as the amount of guidance presented in the specification and the presence of working examples must be considered to determine whether undue experimentation is required to practice the claimed invention. *See, e.g.*, *Ex Parte Forman*, 230 USPQ 546 (Bd.

Pat. App. & Int. 1985) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As described in *Wands*, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Wands*, USPQ2d at 1404, quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982). Moreover, "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP 2164.01 *citing In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984).

As set forth in the Manual of Patent Examining Procedure (MPEP) § 2164.01, "the test of enablement is not whether any experimentation is necessary, but whether… it is undue." Further, the "fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (citations omitted). Finally, claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. *See, e.g., In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971).

The amended claims are directed to methods of identifying inhibitors of angiogenesis using Axl proteins with 95% identity to the full length of SEQ ID NO:4, wherein down regulation of the Axl protein results in inhibition of angiogenesis. The specification provides ample support for these claims. For example, SEQ ID NO:4 is provided, and, to identify proteins with 95% identity to SEQ ID NO:4, well-known sequence analysis algorithms are disclosed at page 11, lines 15-23. Axl was known to be a tyrosine kinase at the time of filing, and therefore, Axl kinase assays can be used to easily identify Axl polypeptides that fall with the scope of the claims.

First, the Office Action alleges that the claims are directed to 25 amino acid fragments of the Axl protein. In order to expedite prosecution, claim 1 is amended to recite the full-length of SEQ ID NO:4. The Office Action also cites a number of references that allegedly demonstrate that even minor modifications of the Axl protein sequence would result in

unpredictable disruption of protein function. Each of the references cited in the Office Action is more than 15 years old.

The Office Action cites O'Bryan *et al.* (1991), which discloses the sequence of the Axl protein with identification of a signal peptide domain, N-linked glycosylation sites, an ATP-binding domain, and autophosphorylation sites believed to be a PtdIns3-kinase binding domain at Figure 2. At Figure 3 O'Bryan *et al.* provides an alignment of the Axl amino acid sequence with 10 other protein kinases and a consensus sequence. Highly conserved amino acids are identified. Figure 4 of O'Bryan *et al.* provides a schematic drawing of the Axl protein and the functional domains of the protein.

The Office Action cites three references that allegedly support the difficulty of predicting whether an amino modification will affect the function of a protein: Bowie *et al.* (1990), Burgess *et al.* (1990), and Lazar *et al.* (1988). According to the Office Action Bowie *et al.* teach that "predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex." Office Action at page 8, citing Bowie *et al.* col. 1, page 1306. In the same paragraph, Bowie *et al.* state that purpose of the article is to ". . . describe how an analysis of allowed amino acid substitution in proteins can be used to reduce the complexity of sequences and reveal important aspects of structure and function." Bowie *et al.* go on to describe a number of studies that determined amino acid function by aligning sequences of related proteins. The alignments were used to identify invariant and conserved residues with functional roles. Bowie *et al.* also disclose methods to select amino acid substitution that are least likely to disrupt function, *e.g.*, substitution of amino acids with similar hydrophobicity, charge, or size. Bowie *et al.* page 1306, right column.

Rather than supporting the allegation of unpredictability, Burgess *et al.* and Lazer *et al.* use the methods of Bowie *et al.* to identify conserved amino acids in proteins and to demonstrate the ease of maintaining or diminishing protein function when modifying amino acids. Based comparison to related protein sequences, Burgess *et al.* identified a conserved lysine (Lys132) in the fibroblast growth factor (FGF) protein and predicted a functional role for Lys132. Burgess *et al.* at page 2130, left column. (The Office Action discusses Lys118.

Applicants believe this is a typographical error, as Lys118 is not discussed in Burgess *et al.*) Burgess *et al.* changed Lys132, a basic amino acid, to glutamic acid, an acidic amino acid. Those of skill would recognize substitution of glutamic acid for lysine as a non-conservative and would predict the disruption of FGF function observed by Burgess *et al.* Similarly, Lazar *et al.* identified two conserved amino acids in the TGF-α protein, based on comparisons to sequences of other members of the EGF-like protein family. Conserved amino acid Asp-47 tolerated some amino acid substitutions, while invariant amino acid Leu-48 did not tolerate the tested amino acid substitutions. Thus, the predictability of amino acid substitution disclosed in Bowie *et al.* is supported by the results of Burgess *et al.* and Lazar *et al.*

The information of O'Bryan *et al.* is readily applicable to the disclosure of Bowie *et al.* O'Bryan *et al.* provide alignments for those of skill to identify invariant and conserved amino acids in the Axl protein and, if desired to modify amino acids in a manner that preserves the protein function.

Finally, Applicants respectfully bring to the Examiner's attention two recent decisions by the Board of Patent Appeals and Interferences: *Ex parte Sun,* Appeal No. 2003-1993 and *Ex parte Bandman*, Appeal No. 2004-2319. In both cases, the board found that claims directed to sequences with 80% or 95% identity to a reference sequence were enabled because the supporting specifications provided a single reference sequence and an assay for activity of the encoded protein. As discussed above, the specification and knowledge in the art provide the Axl amino acid sequence and kinase assays for the recited Axl activity. Thus, based on these recent Board decisions, the claims are enabled.

In view of the above amendments and arguments, withdrawal of the rejection of claims 1-12, 14-19, 53, and 54 for alleged lack of enablement is respectfully requested.

B. Paragraph 9

Claims 27-37, 44, 45, 53, and 54 are rejected for alleged failure to comply with the enablement requirement. The Office Action alleges that the subject matter of the claims is not enabled by the specification. The Office Action alleges that the claims are not enabled because the claims are drawn to identifying "antitumor therapeutics", that there is no "nexus

drawn to Axl and antitumor therapeutics in vivo", and because the art of anti-cancer therapy is "highly unpredictable." The amended claims are directed to an in vivo method for identifying a compound that inhibits angiogenesis. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

First, Applicants remind the Examiner that the claims are method claims and are not directed to compounds, including therapeutic compounds. The claims are directed to methods of identifying compounds that inhibit angiogenesis. Applicants have provided multiple examples of well-known assays to measure angiogenesis, including, *e.g.*, haptotaxis assays, (at page 32, lines 28-32; page 48, lines 25-30; and Figures 11-13), endothelial tube formation assays, (at page 32, lines 28-32 and Figure 17), chick CAM assays (at page 33, lines 17-22), mouse corneal assays (page 33, lines 23-26) and tumor neovascularization assays (at page 33, lines 27-31; page 49, lines 1-20; and Figure 18). Each of these assays serves as an art accepted model of angiogenesis. In addition, results at page 5, lines 22-23; page 48, lines 25-20; and Figures 11-17 serve as working examples for the claimed methods.

According to the MPEP at 2164.02, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating to that condition, unless the Examiner has evidence that the model does not correlate. The issue is whether one of skill in the art would accept the model as reasonably correlating to the condition. *In re Brana,* 51 F.3d 1560, 1566 (Fed. Cir. 1995). In addition, the Federal Circuit has ruled that a rigorous or exact correlation is not required. *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985). The Examiner has provided no evidence that the models disclosed above do not correlate to angiogenesis; therefore, Applicants respectfully request withdrawal of the rejection for alleged lack of enablement.

C. Paragraph 10

Claims 27-37, 40-45, and 53 are rejected for alleged failure to comply with the enablement requirement. The Office Action alleges that claims directed to "a method of identifying a compound that modulates tumorigenesis. . . " are not enabled by the specification. In order to expedite prosecution, independent claim 27 and dependent claims 40-45, and 53 are

amended to recite "a method of identifying a compound that inhibits angiogenesis. . ." In view of this amendment, withdrawal of this rejection for alleged lack of enablement is respectfully requested.

D. Paragraph 11

Claims 27-37, 40-45, and 53 are rejected for alleged failure to comply with the enablement requirement. The reasoning for the rejection appears to identical to the reasoning used to reject claims 1-12, 14-19, 53, and 54 in paragraph 8 of the Office Action. For example, like paragraph 8, paragraph 11 of the Office Action cites O'Bryan *et al.*, Bowie *et al.*, Brugess *et al.* and Lazar *et al.* Applicants traverse this rejection to the extent it applies to the amended claims. Claims 27-37, 40-45, and 53 are amended in a manner similar to that of claims 1-12, 14-19, 53, and 54, and are now directed to methods of identifying inhibitors of angiogenesis using Axl proteins with 95% identity to the full length of SEQ ID NO:4. Applicants direct the Examiner to section IVA of this response for arguments against this rejection for alleged lack of enablement. To supplement those arguments with information specific to the claimed in vivo methods of identifying inhibitors of angiogenesis, Applicants bring to the Examiner's attention disclosure of well-known vascularization assays in the specification including, *e.g.*, haptotaxis assays, (at page 32, lines 28-32; page 48, lines 25-30; and Figures 11-13), endothelial tube formation assays, (at page 32, lines 28-32 and Figure 17), chick CAM assays (at page 33, lines 17-22), mouse corneal assays (page 33, lines 23-26) and tumor neovascularization assays (at page 33, lines 27-31; page 49, lines 1-20; and Figure 18).

In view of the above amendments and remarks, withdrawal of the rejections for alleged lack of enablement is respectfully requested.

V. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 1-12, 14-19, 27-37, 40-44, 45 and 53 are rejected for allegedly failing to meet the written description requirement. According to the Office Action the specification does

not describe the genus of Axl polypeptides used in the claimed methods. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

As currently applied, the specification does comply with US patent law for description of a nucleic acid or amino acid sequence. The Federal Circuit court of Appeals addressed the description adequate to show one of skill that the inventors were in possession of a claimed genus at the time of filing. *See, e.g., Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002). An applicant may also show that an invention is complete by

> . . . disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Id.* at 1613.

Furthermore, "description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." *See, e.g.*, 66 Fed. Reg. 1099, 1106 (2001).

The specification does provide descriptive support for the full scope of the claimed invention by providing both SEQ ID NO:4, a reference sequence for the recited polypeptides, and assays for regulation and inhibition of angiogenesis. Axl kinase activity was well-known at the time of filing. The assays are described throughout the specification, for example, regulation and modulation of angiogenesis and tumorigenesis (at page 1,line 33 through page 2, line 3; page 2, lines 24-28; page 5, lines 3-21; page 6, lines 8-9; page 32, lines 25-32; page 33, lines 15-26; and page 48, lines 23-30; and Figures 11-17), haptotaxis assays, (at page 32, lines 28-32; page 48, lines 25-30; and Figures 11-13), endothelial tube formation assays, (at page 32, lines 28-32 and Figure 17), chick CAM assays (at page 33, lines 17-22), mouse corneal assays (page 33, lines 23-26) and tumor neovascularization assays (at page 33, lines 27-31; page 49, lines 1-20; and Figure 18). This information is more than adequate to meet the written description requirement, particularly in view of *Enzo*, cited above, recent Board decisions, and the interpretation of the Written Description Guidelines evidenced by the USPTO's own Synopsis of Application of Written Description Guidelines.

Applicants again bring to the Examiner's attention the *Sun* and *Bandman* decisions by the Board of Patent Appeals and Interferences. In both cases, the board found that claims directed to sequences with 80% or 95% identity to a reference sequence were described because the supporting specifications provided a single reference sequence, teachings of areas of the claimed sequences that could be modified, and a functional assay for activity of the encoded proteins. Such teachings are included in the present application, as indicated above.

Applicants also direct the Examiner's attention to Example 14 of the Synopsis of Application of Written Description Guidelines, which analyzes a claim directed to a protein with an amino acid sequence at least 95% identical to SEQ ID NO:3 and that has a catalytic activity. In Example 14, the specification provided one example of a protein that was a member of the claimed genus. The Patent Office concluded that the claim of 95% identity to a reference sequence with a specified catalytic activity was adequately described within the meaning of 35 U.S.C. §112, first paragraph. First, the Synopsis reasons that the genus of proteins that must be variants of the claimed SEQ ID NO:3 does **not** have substantial variation since all of the members must have 95% identity to the reference sequence and must have the specified catalytic activity. Therefore, according to the Synopsis, the "single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay. . . " that could be used to identify members of the claimed genus. As described above, the specification discloses the angiogenesis activity of the recited Axl proteins and assays for its measurement. Thus, at a minimum, on the basis of the Synopsis of Application of Written Description Guidelines issued by the USPTO, the present claims that recite 95% identity to SEQ ID NO:4 meet the written description requirement.

In view of the above arguments and amendments, withdrawal of the rejection for alleged lack of written description is respectfully requested.

VI. Rejections under 35 U.S.C. §102

The claims are rejected as allegedly anticipated by the cited references. To the extent the rejections apply to the amended claims, Applicants respectfully traverse the rejections.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found...in a single prior art reference." *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Thus, in order to anticipate, the cited reference must contain every element of the claims at issue. The cited references do not.

A. Healy et al.

Claims 1, 2, 5, 6, 9-11, 14, 19, 53, and 54 are rejected as allegedly anticipated by Healey *et al.*, *Am .J. Physiol. Lung Cell Mol. Physiol.* 280:L1273-L1281 (2001). As amended, independent claim 1 is directed to a method of identifying a compound that inhibits angiogenesis, by contacting the compound with an Axl polypeptide, and determining the functional effect of the compound upon the Axl polypeptide to identify the compound that inhibits angiogenesis.

According to the Office Action Healey *et al.* disclose a method of identifying a compound that inhibits angiogenesis through the Axl polypeptide by contacting a cell that comprises the Axl polypeptide with the Gas-6 protein. Gas-6 is a ligand for the Axl polypeptide. The Office Action indicates that Healey *et al.* determined the effect of Gas-6 by measuring the level of apoptosis in cells that expressed the Axl protein. The Office Action refers to Figures 9 and 10 of Healey *et al.* which show that Gas-6 and Axl have anti-apoptotic activity in the tested human pulmonary artery endothelial cells (HPAEC). However, Healey *et al.* does not demonstrate that Gas-6 inhibits angiogenesis in the HPAEC that comprise the Axl protein. Healey *et al.* disclose that the antiapoptotic activities of Gas-6 are "relevant to endothelial cell survival in the quiescent environment of the vessel wall." *See, e.g.*, Healey *et al.* abstract at page L1273. Thus, Gas-6 activation of the Axl protein is used to promote endothelial cell survival when angiogenesis is not occurring. Therefore, Healey *et al.* does not disclose identification of an inhibitor of angiogenesis using the Axl polypeptide and cannot anticipate the claims.

B. Varnum et al.

Claims 27-37, 44, 45, 53, and 54 are rejected as allegedly anticipated by Varnum *et al.*, *Nature* 373:623-626 (1994). As amended, independent claim 27 is directed to an in vivo method of identifying a compound that inhibits angiogenesis, by contacting the compound with a cell that expresses an Axl polypeptide, and determining the functional effect of the compound upon Axl polypeptide to identify a compound that inhibits angiogenesis.

According to the Office Action, Varnum *et al.* disclose a method for identifying a compound that modulates tumorigenesis by contacting A172 cells that comprise the Axl protein with a compound (either Gas-6 or vitamin K) and determining the functional effect on the cells. The amended claims are directed to in vivo methods of assaying the angiogenesis using cells that express an Axl protein after exposure to a test compound. Varnum *et al.* disclose only methods of purifying Axl from tissue culture cells or assaying Axl effects on tissue culture cells. Varnum *et al.* does not disclose any angiogenesis assay. Because Varnum *et al.* fails to disclose this element of the amended claims, Varnum *et al.* cannot anticipate the claims.

C. Lee et al.

Claim 27 and 40 are rejected as allegedly anticipated by Lee *et al.*, *Mol. Cell. Biol.* 19:8075-8082 (1999). According to the Office Action, Lee *et al.* discloses a method for identifying a compound that modulates tumorigenesis by contacting human ovarian cancer cells that comprise a recombinant Axl protein with Gas-6 and determining Axl activation. However, Lee *et al.* does not disclose a method of assaying angiogenesis. Lee *et al.* determined Axl expression and activation in a human ovarian cancer cell line, not angiogenesis, as is required by the amended claims. Because Lee *et al.* fails to disclose this element of the amended claims, Lee *et al.* cannot anticipate the claims.

In view of the above amendments and arguments, withdrawal of the rejections for alleged anticipation is respectfully requested.

VII. Rejections under 35 U.S.C. §103(a)

The claims are rejected as allegedly obvious by various combinations of references. To the extent the rejections apply to the amended claims, Applicants respectfully traverse the rejections.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP§2143. See also *In re Rouffet,* 47 USPQ2d 1453. The court in *Rouffet* stated that "even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination." *Rouffet* at 1459. The court has also stated that actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, or teaching, or motivation to combine must be "clear and particular." *In re Dembiczak*, 50 USPQ2d 1614, 1617 (1999). Under the standards listed above, the Office Action does not establish a prima facie case of obviousness.

A. Healy et al. in view of Varner and Cheresh, Panzer et al., and Ruoslahti et al.

Claims 12, and 15-18 are rejected as allegedly obvious over Healey *et al.* in view of Varner and Cherish, *Cell Biology* 8:724-730 (1996); Panzer *et al.* US Patent Application Publication 2004/0048253 (2001); and Ruoslahti *et al.* US Patent No. 6,180,084 (2001).

Claims 12 and 15-18 depend from claim 1, which is discussed above. The Office Action applies the analysis discussed above to Healey *et al.* The Office Action asserts that Varner and Cherish disclose that integrin αvβ3 is significantly upregulated on vascular cells and plays a biological role in blood vessel formation and that Panzer *et al.* and Ruoslahti *et al.* teach general method of screening compounds for a desired effect.

Healey *et al.* teaches away from use of the Axl polypeptide to identify compounds that inhibit angiogenesis. Applicants assert that Healey *et al.* teaches that Axl and its ligand Gas-6 have anti-apoptotic activity in the tested human pulmonary artery endothelial cells (HPAEC).

Healey *et al.* disclose that the antiapoptotic activities of Gas-6 are "relevant to endothelial cell survival in the quiescent environment of the vessel wall." *See, e.g.*, Healey *et al.* abstract at page L1273. Thus, according to Healey *et al.* Gas-6 activation of the Axl protein is used to promote endothelial cell survival when angiogenesis is not occurring. Therefore, Healey *et al.* does not teach or suggest use of the Axl polypeptide to identify compounds that inhibit angiogenesis.

The Office Action alleges that Varner and Cherish disclose a role for integrin $\alpha v\beta 3$ in angiogenesis. However, Varner and Cherish do not teach or suggest a role for Axl in angiogenesis and, therefore, cannot be used to cure the deficiencies of Healey *et al.* The other cited references, Panzer *et al.*, and Ruoslahti *et al.* disclose only general methods of screening small molecules and other compounds for a desired effect. No discussion of the Axl polypeptide or a role in angiogenesis is disclosed. Panzer *et al.*, and Ruoslahti *et al.* cannot be used to cure the deficiencies of Healey *et al.* Thus, alone or in combination, the cited references cannot be used to provide a prima facie case of obviousness.

B. Varnum et al. in view of Panzer et al., and Ruoslahti et al.

Claims 41-43 are rejected as allegedly obvious over Varnum *et al.* in view of Panzer *et al.* and Ruoslahti *et al.* The content of the cited references is discussed above. Varnum *et al.* does not teach or suggest in vivo method of identifying a compound that inhibits angiogenesis, by contacting the compound a cell that expresses an Axl polypeptide, and determining the functional effect of the compound upon angiogenesis to identify a compound that inhibits angiogenesis. The general methods disclosed in Panzer *et al.* and Ruoslahti *et al.* fail to cure the deficiencies of Varnum *et al.* Thus, alone or in combination, the cited references cannot be used to provide a prima facie case of obviousness.

In view of the above arguments and amendments, withdrawal of the rejections for alleged obviousness is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

/Beth L. Kelly/

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